

Review

## Anemia: Considerations for the Dental Practitioner

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**Abstract:** Anemia is a condition of decreased red blood cell number or hemoglobin concentration, or of disturbance in their function, ultimately leading to decreased oxygen transport to tissues. Many factors and diseases may lead to anemia, with wide manifestations systemically as well as orally. Therefore, a sound understanding of this syndrome is essential for the dental practitioner, with emphasis on alerting signs, dental management and proper communication with patient's physician.

**Keywords:** Anemia; dental; management; oral manifestations.

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### 1. Introduction

Hemoglobin (Hgb) is a protein rich in iron found in the red blood cells (RBCs). (1) It normally comprises 4 globin chains of 2 types, alpha ( $\alpha$ ) and beta ( $\beta$ ); these chains have the same length but differ by their amino acid sequence. In human's Hgb, embryonic and adult,  $\alpha$  chains are identical. However, other chains include in adults the  $\beta$  Hgb (HgbA,  $\alpha_2\beta_2$ ), the gamma ( $\gamma$ ) chain of fetus (HgbF,  $\alpha_2\gamma_2$ ), and the less-common adult delta ( $\delta$ ) chain (HgbA<sub>2</sub>,  $\alpha_2\delta_2$ ). (2) Hgb binds to

oxygen (O<sub>2</sub>) from the lungs to tissues throughout the body. By definition, anemia is caused by the decrease in the O<sub>2</sub>-binding capability of blood; it can result from: a) decreased erythropoiesis (production of RBCs), b) increased need for iron, c) increased destruction of RBCs, or d) formation of atypical RBCs with Hgb concentration inferior to normal (in men: 13.5 to 18.0 g/dL, in women: 12.0 to 15.0 g/dL, and in children 1.0 to 16.0 g/dL).(1,2)

According to the etiopathogenesis, classification of anemia may include (2–5):

- Blood loss anemia (hypovolemia)
- Iron-deficiency anemia
- Anemia resulting from chronic disease
- Hemolytic anemia: such as glucose 6-phosphate dehydrogenase (G6PD) deficiency
- Hemoglobinopathies: sickle cell anemia (SCA) or thalassemia
- Hypoproliferative anemias: aplastic anemia (AA), folate- or B12- deficiency anemias

Furthermore, according to the RBC size (based on the mean corpuscular volume, MCV), anemias can also be classified into (2):

- Microcytic (MCV <80 fL / cell): Iron-deficiency and thalassemia
- Normocytic (MCV = 80-100 fL / cell): SCA, G6PD-deficiency, AA
- Macrocytic (MCV >100 fL / cell): megaloblastic anemias, such as pernicious anemia (vitamin B12 deficiency), or folate deficiency

## **2. Anemia**

### **2.1. Iron-deficiency anemia**

Iron-deficiency anemia is microcytic, usually hypochromic, affecting around one-third of the worldwide population. Its incidence increases along age, and it is more frequent in women.(1) Usually, it is asymptomatic or mild, in which a case it requires no to minimal treatment.(1) It is caused by low iron intake linked to poor dietary habits, extreme blood loss like in menorrhagia and some gastrointestinal ulcers, or increased demand for iron due to pregnancy or resulting from some chronic diseases such as Crohn's disease, ulcerative colitis, hematological malignancies.(2,6) Iron-deficiency anemia is usually manifested on a complete blood count (CBC) as low serum ferritin, low iron levels, and increased total iron-binding capacity (TIBC), together with a decrease in RBC size (low mean cell volume – MCV) and mean corpuscular hemoglobin concentration (MCHC). In the chronic state, blood smear may show hypochromic RBC.

It is worth contrasting iron-deficiency anemia with anemia of chronic diseases, in which ferritin level is normal, while both circulating iron as well as TIBC are low.

## **2.2. Glucose 6-phosphatase dehydrogenase deficiency anemia**

G6PD deficiency anemia is a hereditary, normocytic hemolytic-type anemia linked to the high rate of destruction of RBCs as a result of oxidative stress. It is the main frequent enzyme disorder occurring especially among Mediterranean, Middle Eastern, and Asian populations.(3) G6PD deficiency disrupts the hexose monophosphate shunt pathway leading to the accumulation of toxic oxidants within RBCs resulting in formation of Heinz-Ehrlich bodies. These bodies hardly circulate through the spleen and liver and are removed by hemolysis. Hemolysis occurs when the affected person's bloodstream is exposed to oxidative substances such as drugs (aspirin, sulfonamides, vitamin K...), fava beans, and infections.(2)

## **2.3. Sickle cell anemia**

SCA is a form of sickle cell disease, an autosomal recessive blood disorder, resulting from defective Hgb synthesis leading to sickle-shaped RBCs with bad oxygenation capability and difficult circulation within capillaries. In fact, sickle-shaped RBCs are rigid and would lead to: a) stasis of blood flow that will accumulate in the spleen where erythrocytes are destroyed by hemolysis, and b) poor blood circulation, leading to an increase of O<sub>2</sub> demand and more sickled RBCs; this vicious cycle is at the origin of a condition known as sickle-cell crisis. SCA preferentially affects populations of malaria-endemic countries (e.g. Africa, USA, and Brazil). The prevalence of SCA in USA ranges between 0.10% and 0.15% and in some regions in Brazil 0.20%. It is to be noted that African Americans followed by the Hispanic Americans are the most affected in USA.(2,7-9)

## **2.4. Thalassemia**

Thalassemia is a genetic disorder that involves atypical Hgb synthesis, consequently defective RBCs.(8,10) It belongs to the microcytic hemolytic type of anemia and comprises two types,  $\alpha$  and  $\beta$ .(2,9) In major thalassemia, the unsuccessful erythropoiesis augments the volume of plasma and progressively leads to a splenomegaly and bone marrow expansion resulting in osteomalacia and craniofacial deformities (Chipmunk facies).(8,11) Additionally, iron absorption and deposition in tissues are increased causing oxidative damages and dysfunction of the heart,

liver, and endocrine glands.(8) Thalassemia is more common among the Mediterranean, Middle Eastern, and South Asiatic populations.(2,8)

## **2.5. Vitamin B12- and folate-deficiency anemias**

Vitamin B12- and folate-deficiency anemias are classified as hypoproliferative and macrocytic. Moreover, both are considered megaloblastic anemias, in which neutrophils are segmented and present disordered DNA synthesis. They result from vitamin B12 and/or folate (formerly known as vitamin B9) deficiencies.(2) In fact, these vitamin B constituents are both essential for erythropoiesis within the bone marrow.(2,12) Usually, vitamin B12 deficiency anemia, referred to as pernicious anemia, is secondary to deficit in intrinsic factor secreted by the gastric mucosa and whose role is to bind to and transport vitamin B12 through the intestine where it is absorbed at the terminal ileum.(13,14) Vitamin B12 deficiency may be linked to certain drugs such as proton pump inhibitors (PPIs) (15) and metformin (16), as well as to celiac and Crohn diseases.(2) Therefore, it may be due to malnutrition, malabsorption or subsequent to other diseases; it is usually chronic and develop over a long time.

On the other hand, folate deficiency anemia is mainly nutritional, related to diets poor in vegetables, meat and fruits (17) or due to defective absorption of folate (due to gastrointestinal disease), in addition cases of chronic alcoholics and substance abusers).(18) Folate- and vitamin B12 deficiencies are not frequent globally. However, it was found that they are exhibited in about 2% of the persons over 60 years of age.(2)

## **2.6. Aplastic anemia**

This is a rare life-threatening idiopathic condition characterized by bone marrow failure and, consequently, pancytopenia (reduction in the three types of blood cells: RBCs, white blood cells (WBCs), and platelets).(19) Pancytopenia presents both rapid onset and progression.(19,20) In some cases, chemicals, radiation, chemotherapy, and autoimmune diseases have been reported to be implicated as etiological factors of AA.(2) The incidence of AA ranges between 2 and 7 per million/year.(21)

## **3. Signs and symptoms of anemia**

Signs and symptoms of anemia differ depending on its etiology and severity. While mild anemia is usually asymptomatic, more severe anemias might include the following symptoms: a)

weakness, b) fatigue, c) pale and yellow skin, conjunctiva, and mucosa, d) arrhythmia, e) dyspnea, f) chest pain, g) dizziness, h) headaches, i) cold hands and feet, j) koilonychias, k) dermatitis herpetiformis, l) petechiae, and m) splenomegaly.(1,4)

#### 4. Diagnosis, laboratory tests and findings, and treatments of anemia

Diagnosis of anemia starts with a detailed medical history and familial diseases, complete physical exam and laboratory work-up: the main laboratory assessment test is the CBC which displays RBC count, ratio of RBCs to total blood volumes (hematocrit), Hgb level, MCV, and through a blood smear to evaluate RBCs size, shape and chromicity.(22)

It is to be noted that, in adults, the normal RBCs count range is: a) 4.7 to 6.1 million cells per microliter (mcL) for men, b) 4.2 to 5.4 million cells per mcL for women, and c) 4 to 5.5 million cells per mcL for children. As for normal adult hematocrit values, they vary between 41% and 50% in men and 36% and 44% in women.(22)

Additional tests to determine the cause of anemias are required and summarized with their respective treatments in Table 1 as proposed by Patton and Glick.(2)

	<b>Specific laboratory tests and findings</b>	<b>Treatment</b>
<b>Iron-deficiency anemia</b>	-Levels of serum ferritin, iron, and iron saturation: low  -Level of total iron-binding capacity and/or transferrin: high	Iron supplementation
<b>G6PD deficiency anemia</b>	-Blood G6PD enzyme levels: decreased  -Blood indirect bilirubin levels: elevated	Avoiding medications that cause oxidation, with and other risk factors
<b>SCA</b>	-Sickle cell test: presence of sickle-shaped RBCs  -Hgb electrophoresis: presence of abnormal Hgbs	-Relieving symptoms and preventing complications (intravenous fluid, O <sub>2</sub> supplementation, pain control, and antibiotics when needed)  -Blood transfusions

<b>Thalassemia (major and minor)</b>	Hgb electrophoresis: elevated levels of HgbF	-Major: transfusions to maintain Hgb levels but with caution for iron overload  -Minor: no intervention is needed
<b>Vitamin B12- and folate-deficiency anemias</b>	-CBC: other than decreased levels of RBCs, abnormal and decreased WBCs and platelets in advanced deficiencies  -Vitamin B12 and folate blood levels: decreased levels of vitamins	- Vitamin B12 supplements in the case of vitamin B12-deficiency anemia  - Folate-deficiency anemia treated with supplementation
<b>AA</b>	Mandatory bone marrow biopsy: decreased blood cells in bone marrow.	-Immunosuppressive therapy  -Blood transfusions  -Stem cells transplant (bone marrow transplant)

**Table 1:** Additional tests of different types of anemia and their treatments.(2)

## 5. Oral manifestations of anemia

Anemia oral manifestations may include the following: a) pallor of the oral mucosa, especially the soft palate and floor of the mouth, b) depapillated and atrophic tongue, c) glossodynia, d) petechiae, e) mucosal ulcers, f) gingival hypertrophy and bleeding mainly in AA, g) jaundice and icteric presentation of the oral mucosa due to hyperbilirubinemia in hemolytic anemias, h) dysphagia and taste aberrations, i) xerostomia, j) angular stomatitis, k) protrusive maxilla and alveolar enlargement as part of the developmental changes in thalassemia major, and l) in SCA, generalized radiolucency in the mandible as a result of marrow hyperplasia.(2,3) Moreover, pernicious anemia may cause neurological disturbances such as nerve paresthesia.

## 6. Risks in the dental office

It is important to refer patients with signs and symptoms of anemia to their primary care physicians. Depending on the severity, elective surgical procedures may be avoided in many instances, as there may be an increased possibility of hemorrhage and poor wound healing in case of low levels of Hgb.

In SCA, antibiotic prophylaxis may be indicated before any invasive dental procedures in uncontrolled cases to prevent possible infection risk.(3,23) Moreover, odontogenic infections

should be rapidly treated with adequate antibiotics in order to avoid infection-related SCA crisis.(2,3) In fact, SCA crisis is a major clinical feature of SCA and described as “acute painful crisis” requiring urgent hospitalization.(24,25)

Dental treatments for patients with AA require close collaboration with patient’s treating physicians; they possibly need antibiotic prophylaxis for those with neutropenia and platelet or hemostatic support for those with thrombocytopenia.(26) Although no clear evidence exists, there is still no consensus on the use of vasoconstrictors with local anesthesia due to concerns of decreased tissue perfusion and hence increased risk of infection and necrosis.(2)

Finally, some medications such as aspirin and penicillin are linked to hemolysis in hemolytic anemias and must be avoided. Additionally, the use of salicylates for pain control in patients with SCA is not recommended because they can trigger an oxidative crisis.(22,26)

In addition to the discussed types of anemia and associated risks, many other forms of anemias exist, with a broad sense of involvement both oral and systemic, such as Fanconi’s anemia, among others. Therefore, any unusual findings that may be related to hematological disorders should be effectively communicated with the patient’s physician, with ultimate emphasis on a thorough medical history and physical examination by the dental practitioner who may be the first to detect signs a silent systemic disease.

## **7. Conclusion**

Anemia, although quite common, may not always present as subclinical with little relevance to dental practice. On the contrary, anemias, even in some mild cases, may lead to wide oral and systemic disturbances as well as serious complications in the unmanaged dental patient.

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